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Renal Abnormalities in Sickle Cell Disease

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Sickle cell anemia and the related hemoglobinopathies are associated with a large spectrum of renal abnormalities. The patients have impaired urinary concentrating ability, defects in urinary acidification and potassium excretion, and supranormal proximal tubular function. The latter is manifest by increased secretion of creatinine and by reabsorption of phosphorus and β_2-microglobulin. Young patients with sickle cell disease (SCD) have supranormal renal hemodynamics with elevations in both effective renal plasma flow (ERPF) and glomerular filtration rate (GFR). These parameters decrease with age as well as following the administration of prostaglandin inhibitors. Proteinuria, a common finding in adults with sickle cell disease, may progress to the nephrotic syndrome. Proteinuria, hypertension, and increasing anemia predict end-stage renal disease (ESRD). While ESRD can be managed by dialysis and/or renal transplantation, there may be an increased rate of complications in renal transplant recipients with SCD. Hematuria is seen in individuals with all of the SCDs as well as with sickle cell trait. In most cases the etiology of the hematuria turns out to be benign. However, there does appear to be an increased association between SCD and renal medullary carcinoma. Therefore, those SCD patients who present with hematuria should initially undergo a thorough evaluation in order to exclude this aggressive neoplasm. Papillary necrosis may occur due to medullary ischemia and infarction. Erythropoietin levels are usually lower than expected for their degree of anemia and decrease further as renal function deteriorates. An abnormal balance of renal prostaglandins may be responsible for some of the changes in sickle cell nephropathy. Acute renal failure is a component of the acute multiorgan failure syndrome (MOFS). Finally, progression of sickle cell nephropathy to ESRD may be slowed by adequate control of hypertension and proteinuria. However, the prevention of the renal complications of SCD will require a cure for this genetic disorder. Am. J. Hematol. 63: 205–211, 2000.

Key words: sickle cell anemia; hemoglobinopathies; renal abnormalities; proteinuria

INTRODUCTION

Many structural and functional abnormalities of the kidney are observed in patients with sickle cell anemia (SS)[1] and the related hemoglobinopathies. These abnormalities are observed along the entire length of the nephron from the glomerulus to the papillary tip. Because the rate of oxygen consumption by the kidney is very high, a rate exceeded only by that of the heart [1], the kidney is especially sensitive to the vaso-oclusion-induced hypoxia that can result from red cell sickling and/or from sickle cell–endothelial cell adhesion. The environment of the renal medulla is characterized by acidosis, hypertonicity, and hypoxia. These factors tend to promote hemoglobin S polymerization and red cell sickling, thereby making this area of the kidney particularly susceptible to changes in oxygen delivery. In this review, we will discuss the pathophysiology and clinical manifestations of the various renal abnormalities in sickle cell disease (SCD).

PATHOLOGY

The kidneys of young SCD patients with normal renal function tend to hypertrophy, generally exhibiting a smooth capsular surface [2]. As these patients age, there is an increasing frequency of chronic renal failure that is

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[1]In this manuscript, SS refers to individuals with homozygous sickle cell anemia, whereas SCD includes not only SS patients, but also individuals with such mixed heterozygous states as SC, SD, and S-β thalassemia. Finally, AS refers to individuals who carry the sickle cell trait.

associated with scarred, shrunken kidneys, the capsular surface ranging from coarsely granular to grossly distorted and scarred [2].

Enlarged glomeruli are noted both at autopsy and at biopsy where they can sometimes be seen with the naked eye [2]. In SCD patients, glomerular size tends to increase with age. By contrast, in normal individuals after early childhood, little relationship is seen between age and glomerular size [2]. On histological examination, these enlarged markedly hypercellular glomeruli exhibit lobulation of the glomerular tuft. Not uncommonly, glomerular changes indistinguishable from those of proliferative glomerulonephritis may occur in SCD patients who have no apparent renal disease [2]. Reduplication of the basement membrane and mesangial proliferation are also seen in this patient population, changes that occur with increased frequency as SCD patients age. In addition, older patients exhibit progressive glomerular fibrosis. Finally, electron microscopy of the glomeruli from SCD patients, even those without evidence of renal dysfunction, have revealed some effacement of the foot processes and local thickening of the basement membrane. These changes tend to be much more prevalent in cases of SCD associated with the nephrotic syndrome.

The earliest lesions in sickle cell nephropathy include glomerular enlargement, perihilar focal segmental glomerulosclerosis, and hemosiderosis [3]. In more advanced disease, other manifestations of glomerular injury occur including a lesion resembling membranoproliferative glomerulopathy [4] and, less frequently, true immune complex nephropathy [1].

Over the past several years, a number of transgenic mouse models of sickle cell disease have been developed. Among the most severe is the SAD mouse [5]. This mouse, which bears the human α-globin gene and the HbS mutation, $\beta^{6\ glu\rightarrow val}$, also contains two other β-globin gene mutations that greatly enhance the tendency of its hemoglobin to polymerize. The renal pathology of the SAD mouse shows many striking similarities to the human sickle cell nephropathy including both glomerular hypertrophy and mesangial glomerulosclerosis, changes that increase in frequency and severity as the mice age. Other renal changes in these animals include hemosiderosis, cortical infarcts, and papillary necrosis.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Sickle cell nephropathy encompasses a large spectrum of renal abnormalities [1,2]. Much of the pathophysiology of sickle cell nephropathy can be predicted by an understanding of the mechanisms of hemoglobin S polymerization and cell sickling. The renal medulla is composed of renal tubules and medullary blood vessels which are collectively referred to as the vasa recta system. Conditions in this area of the kidney are particularly conducive to hemoglobin S polymerization and erythrocyte sickling. These events, in turn, produce vaso-occlusion within the vasa recta. By contrast to kidneys from normal individuals, microradioangiographic studies performed in kidneys obtained from patients with SCD revealed an almost complete loss of the vasa recta [6], the few remaining medullary blood vessels having a spiral configuration. In addition, they are markedly dilated and appear to end blindly. These changes, while most marked in SS patients, also occur in mixed heterozygotes with the various other SCDs and even in individuals with sickle cell trait (AS).

ABNORMALITIES OF DISTAL NEPHRON FUNCTION

Hyposthenuria, an inability to concentrate urine maximally, is the most frequent clinically recognized renal abnormality in SCD patients [7]. This urinary concentrating defect becomes apparent at an early age in SS individuals. The renal concentrating defect in sickle β-thalassemia may be as prominent as in sickle cell anemia, although in this and in the other SCDs, as well as in sickle cell trait, the concentrating defect becomes manifest much later in life [8,9]. After an 8–10 hr overnight water deprivation, the urine osmolality in SS patients was 414 ± 10 mmol/kg (mean ± SE), considerably lower than the values in normal subjects (911 ± 39 mmol/kg) [10]. Urine concentration does not increase further following vasopressin administration, thereby ruling out central diabetes insipidus [11]. Red cell transfusion can often ameliorate the concentrating defect in SS patients up to the age of 15, but it has little effect in older individuals [8]. However, anemia per se is not responsible for hyposthenuria, as patients with anemia of other etiologies respond normally to water deprivation [12]. Finally, this urine concentrating defect has been noted to develop in a normal donor kidney following its transplantation into a sickle cell patient with end-stage renal failure [13].

The ability to concentrate urine in a normal manner depends upon the structural integrity of the loops of Henle as they course through the hypertonic environment of the renal medulla. Hyposthenuria in SCD is primarily due to loss of deep juxtamedullary nephrons that are necessary for maximal urine concentration. Because the outer medulla is relatively spared, these patients are generally capable of concentrating their urine to the extent required under normal circumstances [6]. However, under conditions of substantial water deprivation and/or volume loss, more rapid and severe volume contraction may ensue.

In individuals with the sickle cell trait, the severity of hyposthenuria is heterogenous and is determined by the percentage of HbS, which in turn is related to α-globin

genotype [14]. Those HbAS individuals who have a normal α-globin genotype (αα/αα) have less urinary concentrating ability than do those with −α/αα or −α/−α genotypes, thereby suggesting that intracellular HbS polymer does influence the pathophysiology of HbAS.

Urine acidification and potassium excretion also take place primarily in the renal medulla. Defective urinary acidification has been reported in SCD patients [9,15]. Acidification of the urine in the distal nephron depends upon the maintenance of a high tubule-to-lumen proton gradient. This is an energy-dependent process which is compromised by medullary ischemia [7]. Decreases in the rates of excretion of titratable acid, ammonia, and total hydrogen ion have been described in SS patients, but the primary abnormality in the acidification defect is an incomplete distal tubular acidosis [1]. This may be due to an inability of the collecting duct to maintain a hydrogen ion gradient. The severity of this defect has been, at least in part, related to the severity of the reduction of concentrating ability [1]. Despite this acidification defect, SS patients are rarely acidotic unless stressed by an additional acid load.

Defects in potassium (K) excretion have been described in SS patients despite normal aldosterone and renin responses [16]. This defect in K secretion is not clinically apparent under normal circumstances, as SS patients usually have a normal serum K concentration. Furthermore, despite an impairment in K excretion, the serum K level does not generally increase even with K loading [16], an observation that may be related to a shift of K from the extracellular to the intracellular compartment. Hyperkalemia, however, often does become apparent with progressive renal insufficiency. Furthermore, SS patients are at risk for increased levels of serum K following the administration of such drugs as angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and K-sparing diuretics [7].

SUPRANORMAL PROXIMAL TUBULE FUNCTION

Several abnormalities in proximal tubular function have been described that appear to have no pathological significance. These include increased reabsorption of phosphate and β_2-microglobulin, and increased secretion of uric acid and creatinine [7]. For this latter reason, creatinine clearance significantly overestimates the rate of glomerular filtration (GFR) in SS patients. In a group of these individuals, as much as a 30% discrepancy was observed when creatinine clearance was compared to inulin clearance, the latter being a much more accurate marker of GFR [10]. It still remains uncertain as to whether this enhanced proximal tubular function produces clinically important changes in the pharmacokinetics of drugs in which renal tubular secretion is a major pathway of elimination (e.g., penicillin and cimetidine) [7].

HEMODYNAMIC CHANGES

Young SCD patients have supranormal renal hemodynamics. Their effective renal plasma flow (ERPF) is elevated, and even when measured accurately, their GFR is increased [10]. Furthermore, they have a decreased filtration fraction indicating that the increase in ERPF substantially exceeds the increase in GFR. Both GFR and ERPF decline toward normal during adolescence and fall to subnormal levels as SS patients age [17–19]. Because of the increased rate of creatinine secretion by the proximal tubules, SS patients may actually have a significant deterioration in renal function long before it is detected by traditional clinical measurements (e.g., creatinine clearance).

The pathophysiological factors which cause alterations in GFR and ERPF appear to result from altered glomerular autoregulation, a change that affects the tone of both the afferent and efferent arterioles. Prostaglandins have been shown to be important mediators of altered glomerular function in SS patients [20]. NSAIDs, for example, do not produce changes in the GFR and ERPF in normal individuals but do cause a predictable fall in these parameters in SS patients [10]. This observation suggests that glomerular function in SS patients is maintained, at least in part, by prostaglandin-mediated afferent arteriolar vasodilation. This increase in prostaglandin synthesis is thought to be related to ischemic damage to the renal medulla [20].

GLOMERULAR ABNORMALITIES

The alterations in glomerular structure and function that are found in sickle cell nephropathy may be similar to those found with the glomerular hypertension that appears in rodents following partial ablative nephrectomy [21,22]. At the time of autopsy, a pathological examination of the kidney remnants revealed perihilar focal and segmental glomerulosclerosis. These changes were ameliorated by ACE inhibitors, presumably through dilation of the efferent arterioles [23]. On the basis of this concept, Falk et al. found that a brief course of enalapril decreased urinary protein excretion in 10 SCD patients with early manifestations of sickle cell nephropathy [3]. While the exact pathogenesis of this glomerular abnormality still remains to be defined, a number of potential etiologic factors exist. These include mesangial phagocytosis of sickled cells [4]; immune complex glomerulonephritis due to autoantigens released from ischemic tubules [24]; glomerular injury caused by hyperfiltration [25]; and glomerular hypertrophy [26].

The most common clinical manifestation of glomeru-

lar injury in SCD is proteinuria which often progresses to the full-blown nephrotic syndrome [1]. In a prospective study, 40% of SS patients with nephrotic syndrome eventually went on to develop end-stage renal disease [27].

Survival into adulthood of SCD patients is marked by an increased incidence of multi-organ dysfunction. Renal insufficiency is reported to occur in 4–18% of SCD patients, the frequency depending at least in part on the genotype [3,4,10,27]. Furthermore, the risk for renal failure in SS patients is increased in those individuals who carry the Central African Republic (CAR) β^s-gene cluster haplotype [27]. Patients with SS disease develop renal failure at a significantly younger age than patients with HbSC disease. Powars et al., in a prospective study of SCD patients, showed that the median age of onset of renal insufficiency was 23 years for SS patients, compared with a median age of 50 years for patients with HbSC disease [27]. Such manifestations as hypertension, proteinuria, increasingly severe anemia, and hematuria predict renal failure in SS patients [27]. Furthermore, once significant azotemia becomes apparent, it rapidly progresses to ESRD. Survival after the onset of ESRD is approximately 4 years [27].

HEMATURIA

Hematuria is one of the most common renal abnormalities in the Sickle Hemoglobin Opathies, occurring not only in SCD patients, but also in individuals with AS. The bleeding appears to occur as a consequence of hemoglobin S polymerization and erythrocyte sickling within the renal medulla. In some cases, the hematuria is caused by papillary necrosis, a condition that can be diagnosed radiologically (see below). The bleeding comes from the left kidney in about 80% of cases [28]. It is bilateral in only a small minority of individuals. In rare instances, sickle cell hematuria may be quite massive with the passage of clots and severe anemia.

The management of hematuria is usually conservative, with bedrest, maintenance of high urinary flow, alkalinization of the urine, and, when necessary, blood transfusion. Vasopressin and epsilon-amino caproic acid (EACA), an antifibrinolytic agent, have both been used with variable success [29,30]. However, caution must be exercised when using EACA as it can predispose to clot formation and obstruction of the urinary system. In cases of prolonged, life-threatening hematuria, unilateral nephrectomy may be performed, although this should always be considered as a treatment of last resort.

Another cause of hematuria in sickle cell patients is renal medullary carcinoma. This is a rare and very aggressive malignancy which has been described in young individuals with both SCD and AS [31–35]. Davis et al. [31] described 22 male and 11 female patients aged 11–39 years old with renal medullary carcinoma. Twenty-five of the patients were black, nine were known to have sickle cell trait, and one had hemoglobin SC disease. These tumors tend to be metastatic at the time of diagnosis, and a mean survival time of 15 weeks from the time of diagnosis testifies to the highly aggressive nature of the tumor [31].

While the etiology of hematuria in SCD or AS is, in most cases, benign, the association between SCD and renal medullary carcinoma makes it important to perform a thorough evaluation in those SCD patients who present with hematuria.

PAPILLARY NECROSIS

Papillary necrosis is associated with all of the SCDs as well as with sickle cell trait. The propensity for these individuals to develop papillary necrosis is thought to be related to obstruction of the microvasculature in the vasa rectae with resulting medullary ischemia and infarction. Papillary necrosis is typically associated with hematuria. In addition, sloughing of the renal papillae can occasionally produce obstruction to urine outflow and renal failure [7].

RENAL HORMONES

Erythropoietin levels are generally increased in steady state SS patients, although rarely to the level that one would expect for the given degree of anemia [36]. With the impaired renal function that often develops in older patients, erythropoietin levels fall [36,37]. Relative erythropoietin deficiency is, therefore, a contributing factor to the anemia observed in these individuals [37]. In addition to renal damage, the failure of erythropoietin levels to increase appropriately in response to anemia in SS patients may be related to the right-shifted hemoglobin–oxygen dissociation curve that is often found in these individuals [38]. Finally, SS patients may require substantially higher doses of erythropoietin than are needed in patients with other forms of ESRD [39].

Plasma renin and aldosterone levels are often elevated in SS patients, not only in volume-depleted conditions but also in the steady state [16].

Indirect measurements of renal prostaglandin activity have been conducted in SS patients by observing the effects of indomethacin, the prostaglandin synthesis inhibitor, on renal hemodynamics and on sodium and water excretion. Following administration of indomethacin, GFR and ERPF fell significantly in SS patients but remained unchanged in control subjects [10]. These studies suggest that prostaglandins are important in maintaining the supranormal levels of GFR and ERPF that are observed in SS patients. In addition, direct analyses of prostaglandin activity have been made by measuring renal prostaglandin excretion in SS patients [40]. In these latter

studies, urinary pGE_2 excretion was found to be normal, while that of $pGF_{2\alpha}$ was decreased. Thus, SS patients exhibit a high pGE_2:$pGF_{2\alpha}$ ratio [40], an abnormal balance that may be responsible for some of the characteristics in sickle cell nephropathy.

ACUTE RENAL FAILURE

Acute renal failure has been described as a part of the multiorgan failure syndrome (MOFS) in patients with SS disease [41]. This syndrome is manifest by the sudden onset of severe dysfunction of at least two major organ systems (i.e., lung, liver, and kidney) in the setting of an acute sickle cell pain episode. The pathophysiology of MOFS is unclear but is almost certainly due, at least in part, to diffuse, microvascular occlusion and tissue ischemia with subsequent organ dysfunction. The renal failure in MOFS may also be related to nontraumatic rhabdomyolysis, a phenomenon which has also been described in SCD patients without MOFS [42,43]. Finally, acute renal failure has been described in association with exertion-induced rhabdomyolysis and DIC in young males with AS [44,45].

TREATMENT

The improved medical care for individuals with SCD has clearly prolonged their survival. As a consequence, the SCD patient population is also exhibiting more end-organ damage, a good example of which is sickle cell glomerulopathy. Glomerular dysfunction in SCD patients frequently progresses to ESRD, a change that is often heralded by increasing proteinuria, worsening anemia, and/or the appearance of hypertension. While no treatment has as yet proven to be effective for sickle cell glomerulopathy, the amount of proteinuria in SCD was observed to fall by over 60% following a brief course of ACE inhibitor therapy [3]. As this observation has now been confirmed in a second short-term study [46], it would be appropriate to test the notion that the progression of SCD glomerulopathy can be halted by a more prolonged course of an ACE inhibitor.

When given to SCD patients, nonsteroidal antiflammatory agents (NSAIDs) can produce significant declines in creatinine clearance and in the rates of glomerular filtration and renal blood flow [47]. Because NSAIDs can also increase the rate of progression to ESRD, these agents should be avoided in those SCD patients with evidence of sickle cell nephropathy.

As effective treatment of hypertension has been reported to delay the progression to ESRD in SCD patients [48], careful attention to blood pressure control is quite important in this clinical setting. SCD patients can generally be treated like other adults with hypertension, although diuretics can be hazardous in this setting and most people therefore tend to avoid their use [48]. Like any other individuals who develop ESRD, the treatment modalities available to SCD patients include dialysis (i.e., hemo- or peritoneal dialysis) and renal transplantation. An early report suggested that the two-year survival rate of SCD patients on dialysis was approximately 60% [49]. The authors attributed this relatively poor outcome to the high frequency of such pre-existing complications as cardiac and pulmonary dysfunction. Additionally, many dialysis-dependent SCD patients experience severe anemia, a problem that is related, at least in part, to their accelerated rate of red cell destruction. While some of these individuals do respond to high doses of erythropoietin, many others remain transfusion-dependent [39].

Renal transplantation for SCD patients with ESRD became a valid alternative to chronic dialysis following a 1978 report by Spector et al. which described a woman with SCD who exhibited excellent renal function 2 years after undergoing transplant surgery [13]. While some reports have indicated poor allograft survival as well as a variety of disease-specific problems, others have found graft and patient survival rates comparable to those of other nondiabetic ESRD patients [50]. A study by Ojo et al. in which patient and allograft outcomes in SCD patients with ESRD were compared to age-matched African-American kidney transplant recipients with other causes of ESRD found comparable short-term allograft results in the two groups [51]. However, beyond 1 year, there was a somewhat shorter cadaveric graft survival and a greater adjusted 3-year risk of graft loss in the sickle cell nephropathy group. Additionally, the authors observed a trend toward improved survival when renal transplantation was compared to chronic dialysis in patients with ESRD secondary to sickle cell nephropathy.

While many SCD patients have done well following renal transplantation, certain complications have been described that, at least in some cases, appear relatively unique to patients with SCD. For example, despite the fact that the patient described by Spector et al. had excellent renal function, she experienced a resumption of frequent acute vaso-occlusive crises [13]. These painful episodes, which began less than 3 months following the surgery, were attributed to the increase in whole blood viscosity that accompanied the higher hematocrit level. Donnelly et al. described a patient who experienced acute renal infarction 6 days following the transplant procedure, an event that was sufficiently severe to require removal of the transplanted kidney [52]. Rather than cellular rejection, the microvasculature of the recently transplanted kidney was filled with sickled red cells, and the kidney itself exhibited multiple small areas of infarction, changes thought secondary to hemoglobin S polymerization, cell sickling, and vaso-occlusion. In yet another single case report, Miner et al. described the appearance of sickle cell nephropathy in the donor kidney, an abnor-

mality that developed 3½ years after a renal transplantation [53]. It is possible that these as well as other sickle cell-related complications could be prevented by the prophylactic administration of hydroxyurea and/or by exchange transfusion in the post-transplant setting [54]. In addition, the availability of new immunosuppressive agents may further improve the outcome following renal transplant in the SCD patient population.

Despite these various therapeutic modalities, the true prevention for sickle cell nephropathy and subsequent ESRD as well as for all of the other complications of SCD ultimately depends upon the development of an early cure for this genetic disorder. Until gene therapy fulfills its enormous promise, the only currently available modality that is capable of curing SCD is bone marrow transplantation (BMT) [55]. However, the availability of BMT is quite limited. First, suitable donors are available for less than 30% of affected individuals. Additionally, the toxicity of the various preparative regimens, the complications of the transplant procedure itself, and the risk of subsequent graft-versus-host disease, together limit the enthusiasm for BMT. This is particularly true in the case of young, relatively healthy SCD patients who have yet to develop much in the way of end-organ dysfunction. On the other hand, these are exactly the patients to whom curative therapy must be applied if sickle cell nephropathy as well as damage to other organs is to be prevented. Perhaps by performing β^s gene cluster haplotype screening and using this technique to identify those young children who are at the highest risk for severe disease, it might be possible to select the most appropriate candidates for BMT long before end-organ damage becomes manifest [56].

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